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BRIEF REPORT

Estimation of Potential Gain in Quality of Life from Early Detection of Cervical Cancer

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ABSTRACT

Objective: To estimate the lifetime gain in the health-related quality of life (HRQOL) from early detection of cervical cancer. **Methods:** A consecutive, cross-sectional sample of 421 patients with cervical cancer was administered the World Health Organization Quality of Life-brief version questionnaires. A nationwide sample of 22,543 patients with invasive cervical cancer (ICC) was collected from the national cancer registry for estimation of lifetime survival function from 1998 to 2007, which was further multiplied by the ratio of HRQOL score functions for patients with ICC and patients with carcinoma in situ (CIS), and summed up over lifetime to obtain expected relative-quality-adjusted survival. The difference between lifetime survival and the expected relative-quality-adjusted survival gives the expected total dissatisfied time during the life course. **Results:** In comparison with patients with CIS postconization, patients with ICC showed consistently lower scores in the physical and psychological domains and that of sexual life after adjustment for other risk factors. The expected years of life lost for an invasive cancer was 6.48 years using the general population as the reference cohort, while the durations of equivalent to living with a very dissatisfied HRQOL were 1.71 and 0.25 for the physical and psychological domains, respectively, and 1.47 years for sexual life. Validation of the extrapolation method based on a subcohort followed from the 6th to the 13th year shows a relative bias of 0.4%. Sensitivity analysis with 37,000 CIS cases as the reference cohort yields a similar result. **Conclusions:** Early detection of cervical cancer not only avoids premature mortality but also prevents long-term living under lower HRQOL scores, including sexual life.

Keywords: cervical cancer, living with very dissatisfied HRQOL, health-related quality of life (HRQOL), relative-quality-adjusted survival.

Introduction

Cervical cancer is one of the most prevalent types of cancer in women and is responsible for 528,000 annual cases worldwide [1]. As a result of widespread screening programs coupled with advanced medical treatment technology, women with cervical cancer now have relatively high 5-year survival rates [2], and there is a consensus that early detection of cervical cancer can avoid premature mortality [3]. The Taiwanese government launched a nationwide cervical screening program in July 1995 in which annual Papanicolaou test screenings were offered to women older than 30 years. Recent records from 2009 indicate that the compliance rate for Papanicolaou test is approximately 50% by age 65 years, which drops down to 30.5% at age 70 years or older [4]. As the life expectancy is about 20 years for an average case of invasive cervical cancer (ICC) in Taiwan [5], the potential long-term gain in the health-related quality of life (HRQOL) may create additional incentives for cancer treatment and screening [6]. Although there are studies exploring the HRQOL for different treatment modalities among patients with ICC [7–10], few have quantified the duration of potential gain in the HRQOL from direct comparison with patients with carcinoma in situ (CIS).

In this study, we recruited patients with CIS postconization as the reference group and performed repeated measurements on the HRQOL after diagnosis during the management of ICC. Finally, we integrated with the survival function of the ICC cohort to estimate the average durations of living under reduced satisfaction of the HRQOL.

Note. Both Jung-Der Wang and Ya-Min Cheng contributed equally to this work.

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Methods

Collection of Sampled Subjects and Quality-of-Life Data

The study commenced after the approval of the institutional review boards of the National Cheng Kung University Hospital (NCKUH, institutional review board no. ER-100-314 and B-ER-102-034). Written informed consents were obtained from every subject. Women with a diagnosis of CIS or ICC who visited the gynecological cancer clinic at the NCKUH were invited to participate in the study. The study was conducted from March 2012 to September 2012. The subjects were receiving treatment and were regularly followed at outpatient clinics. To increase the sample size, repeated measurements were taken from some subjects about 3 months apart.

According to the treatment guidelines of the NCKUH [11] for ICC, patients with early stages of cervical cancer (stage less than IIa) are treated with surgery with radical hysterectomy plus bilateral pelvic lymph node dissection. Patients who had an advanced stage ICC, the medically inoperable, or elderly patients older than 65 years were treated with radiotherapy only or concurrent chemoradiation. Postoperative adjuvant radiotherapy or chemotherapy was given to patients with high risk factors for recurrence, including deep stromal invasion, lymphovascular space invasion, and lymph node metastasis, which were detected from postoperation pathological reviews. Thus, there were four groups according to their primary treatment: CIS postconization, ICC treated with surgery only, those treated with surgery plus chemotherapy or radiotherapy, and those treated with chemotherapy or radiotherapy only.

The Taiwan brief version of the World Health Organization Quality of Life–brief version (WHOQOL-BREF) was used to measure changes in quality of life [12]. The WHOQOL-BREF is an internationally validated instrument for gynecologic cancer [13,14] and is designed to assess physical, psychological, social, and environment domains that affect quality of life. The method of application, the scoring procedures, and the reference time point (during the last 2 weeks) were the same as those of the original WHOQOL-BREF [12]. Individual items were scored from 1 to 5 and summed up with similar items to obtain a domain score: for example, physical score. Each domain was transformed to the same range, from 0 to 100, with higher scores indicating a better quality of life [12]. Each subject was assessed by research assistants who were formally trained in evaluating the HRQOL. Demographic and health information was obtained through the questionnaire, including age at diagnosis, education, marital status, and duration-to-date, as well as comorbidities, including stroke, heart disease, diabetes mellitus, liver disease, hypertension, gastrointestinal disease, musculoskeletal disease, renal disease, and other cancer. Clinical stage, pathology, and different treatments (operation, chemotherapy, or radiotherapy) were abstracted from medical records as predictors of the HRQOL [7,15–17]. The duration-to-date for each measurement was defined as beginning on the first day after diagnosis and ending on the date of interview.

Establishing the Cervical Cancer Cohort for Survival Analysis

A nationwide sample of 37,000 cases of CIS and 22,543 cases of ICC was collected from the national cancer registry during the period 1998 to 2007. Death certificates from the National Mortality Registry were linked to this data set to determine whether each patient was still alive or censored on December 31, 2010. We applied the Kaplan-Meier (K-M) method to estimate survival for these patients from the onset of diagnosis [18] and used a semi-parametric extrapolation method to estimate lifelong survival function, which borrows additional information from age- and sex-matched referents [19] under the assumption of constant excess hazards [20]. The estimates were obtained using iSQoL software, which can be freely downloaded from the Web [21]. Detailed methods and mathematical proofs were described in previous studies [18–20,22,23]. After 13 years of follow-up, the K-M's estimate of average survival of 37,000 cases of CIS was 146.8 months, whereas that of age- and sex-matched referents generated from the life table of Taiwan was 146.4 months. Moreover, because patients with CIS could be cured completely, we assumed that their survival function after the end of the 13th year is the same as that for the general population in Taiwan. The expected years of life lost (EYLL) was estimated by calculating the difference in life expectancy between the invasive cancer cohort and the age-matched referents simulated from the life table of general population of Taiwan.

Estimation of Lifetime Living with Dissatisfied HRQOL

We applied a kernel smoothing method to the measured domain and facet scores from cross-sectional samples for ICC and CIS cohorts to obtain separately estimates of lifetime HRQOL functions [22]. To further quantify the HRQOL reduction in patients with ICC, we defined a quality-of-life measure of relative HRQOL score functions between patients with ICC and CIS, which is the score ratio at time t, for a specific item (domain or facet). If the average HRQOL score of patients with ICC is smaller than that of those with CIS at time t, the ratio, usually a number between 0 and 1, can be interpreted as relative satisfaction of life at that time point for patients with ICC compared with patients with CIS. Although the integration of survival function throughout life is the expected lifetime survival, the integration of the product of survival function and the relative HRQOL functions gives the expected relative-quality-adjusted survival (RQAS), which is equivalent to the duration of living with full satisfaction as an average person with CIS. The difference between lifetime survival and expected RQAS in a psychometric item can be interpreted as the expected total duration of living under a condition equivalent to a very dissatisfied state in that item after the diagnosis of ICC (see Appendix for details of derivation of this formula in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.02.006). We could obtain the estimates by using iSQoL software [21].

Validation of Extrapolation Method and Sensitivity Analysis for Our Estimates

To validate our extrapolation method, we selected a subcohort of patients with ICC between 1998 and 2003, and then extrapolated them to the end of 2010 with the same semiparametric method, which was compared with the K-M estimates of the actual follow-ups. Given the K-M estimate as the criterion standard, we calculated the relative bias for the extrapolation, defined as follows: RB = (Estimate from extrapolation − K-M estimate)/K-M estimate. Moreover, using CIS as the reference population, we conducted sensitivity analyses to estimate the EYLL and expected durations of dissatisfied years for ICC.

Statistical Analysis

Mixed-effects models were constructed assuming a linear autocorrelation for repeated measurements within individual subjects by using the scores for each domain and individual item as the dependent variables, while age at interview, education (>9 years/≤ 9 years), duration after diagnosis, aforementioned comorbidities (yes/no), and marital status (yes/no) served as independent predictive variables. Patients classified in the CIS postconization group were used as the reference group to explore the HRQOL changes for different treatments of cervical cancer. A value of $P < 0.05$ was regarded as significant. All data were collected and analyzed using version 9.2 of SAS software (SAS Institute, Cary, NC).

Table 1 – Demographic characteristics of patients with cervical cancer in the National Cheng Kung University Hospital (NCKUH) and those registered in the cancer registry in Taiwan.

Characteristic	Cancer registry (N = 59,543)	NCKUH (N = 421)	NCKUH (N = 507 measurements)*
Years of follow-up	1998–2007	2012	2012
Mean age ± SD (y)	51.35 ± 14.57	50.4 ± 10.8	53.6 ± 11.8
Carcinoma in situ	37,000	169	190
Invasive cancer, n (%)			
Squamous cell carcinoma	17,868 (79.3)	198 (78.6)	248 (78.2)
Adenocarcinoma and others	4,675 (20.7)	54 (21.4)	69 (21.8)

*Including 86 repeated measurements among the original 421 patients.

Results

The mean duration-to-date was 64.5 months. A total of 421 patients were successfully recruited to complete the HRQOL assessment. Sixteen percent of the patients (n = 67) refused to undergo the HRQOL assessment. Of the 421 patients, 169 were those with CIS and the rest were those with ICC (Table 1). Eighty-six patients (20.4%) were assessed twice roughly 3 months apart: 65 and 21 patients had ICC and CIS, respectively. As indicated in Table 1, the demographic characteristics between the study subjects and subjects in the Taiwan Cancer Registry were similar.

Compared with patients with CIS, all average scores of facets in the WHOQOL-BREF of invasive cancer showed a consistent negative sign (namely, decreased scores), and patients with ICC treated with surgery and/or chemotherapy or radiotherapy showed the lowest scores in both the physical and psychosocial domains and sexual life after controlling for different predictors in the constructed models of mixed effects (Tables 2 and 3). Given general population as the reference group, the EYLL for an invasive cancer was 6.48 ± 0.03 years, while the expected very dissatisfied time during the life course for the physical and psychological domains was 1.71 and 0.25 years, respectively, and for sexual life was 1.47 years (Figure 1). The validation result for the semi-parametric method shows that the relative biases of extrapolation from the end of the 6th to the 13th year was 0.4%. We further conducted a sensitivity analysis using all 37,000 cases of CIS as the reference for estimating the lifetime survival function, which shows 7.11 ± 0.04 years of EYLL; the expected very dissatisfied durations were 1.79 and 0.26 years, respectively, for the physical and psychological domains, and 1.53 years for sexual life.

Discussions

Few of the previous studies exploring the HRQOL changes under different treatments for ICC used patients with CIS for score comparison [7–10,17]. Because HRQOL is generally influenced by different educational levels and socioeconomic states, and cervical cancer is associated with human papilloma virus infection [7,16], there might be a potential selection bias and/or incomparability of contrasted populations [24] if the general population were used as referents. Thus, we deliberately selected patients with CIS for comparison and constructed mixed-effects models to comprehensively control potential confounders, including a subject's education, marital status, age, and other comorbidities. After adjustment for confounding factors, our study found a higher score for patients with a higher education level and lower scores for those comorbid with end-stage renal disease, which corroborated with previous studies [15–17]. Patients with ICC had consistently lower HRQOL in all domains and items if compared with patients with CIS postconization, especially in pain/discomfort, negative feelings, self-esteem, and satisfaction with sexual life, as also reported in previous studies [7,9,10,15,25,26] (Tables 2 and 3). Because a sensitivity analysis using CIS as an alternative reference population to estimate lifetime survival function shows

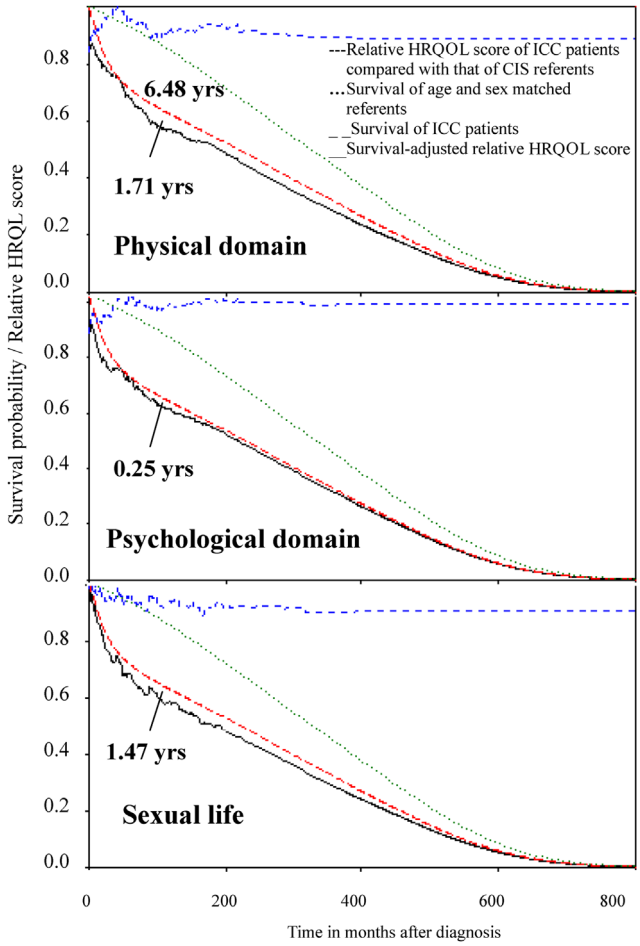

Fig. 1 – The expected years of life loss (EYLL) and the potential gain in health-related quality of life (HRQOL) for early detection of cervical cancer. Each panel illustrates the sum of EYLL (the area between the dotted and long-dashed curves) and the duration of living with very dissatisfied HRQOL in years (the area between the long-dashed and solid curves) for patients with invasive cervical cancer (ICC) and physical and psychological domains and facet of sexual life (the score of ICC was first divided by that of carcinoma in situ [CIS] or referents to obtain the relative HRQOL, or, scores ratio, indicating the degree of satisfaction with HRQOL in comparison to patients with CIS, shown as the dotted curve).

Table 2 – Demographic characteristics and comparison of health-related quality of life from four domains with overall score ratings in patients with cervical cancer based on the WHOQOL-BREF (mean ± SD) (N = 507).

Characteristic	Carcinoma in situ postconization (N = 190)	Surgery only (N = 137)	Surgery plus chemotherapy or radiotherapy (N = 125)	Chemotherapy or radiotherapy only (N = 55)
Mean age ± SD (y)	45 ± 12	47 ± 10	49 ± 9	60 ± 11
Stage 0, n (%)	190 (100)	0	0	0
I–IIA	0	137 (100)	110 (88)	27 (49)
IIB–IIIA	0	0	10 (8)	16 (29)
Others	0	0	5 (4)	12 (22)
Pathology, n (%)				
Carcinoma in situ	190 (100)	0	0	0
Adenocarcinoma	0	23 (17)	21 (17)	4 (7)
Squamous cell carcinoma	0	112 (82)	89 (71)	47 (86)
Others	0	2 (1)	15 (12)	4 (7)
Education <9 y, n (%)	102 (54)	76 (55)	66 (53)	32 (60)
Married, n (%)	148 (78)	110 (80)	97 (78)	47 (86)
Duration ± SD (mo)	66 ± 66	65 ± 59	66 ± 55	62 ± 68
Q1 overall QOL, mean ± SD	3.5 ± 0.7	3.4 ± 0.7	3.3 ± 0.8	3.4 ± 0.7
Q2 overall health, mean ± SD*	3.4 ± 0.8	3.0 ± 0.9	3.1 ± 0.8	3.2 ± 0.8
Physical, mean ± SD†	69.7 ± 12.4	64.1 ± 15.3	64.2 ± 16.1	65.9 ± 16.7
Psychological, mean ± SD†	65.1 ± 14.1	60.0 ± 16.2	59.0 ± 17.2	60.0 ± 17.4
Social (Taiwan), mean ± SD	62.3 ± 15.0	61.6 ± 14.6	62.7 ± 15.6	58.7 ± 16.9
Environmental (Taiwan), mean ± SD	67.4 ± 11.7	65.4 ± 11.7	64.9 ± 11.9	64.6 ± 14.2

QOL, quality of life; WHOQOL-BREF, World Health Organization Quality of Life–brief version.
*One-way analysis of variance: There was a significant difference in four groups, and Tukey post hoc comparisons showed a significant difference between the groups of carcinoma in situ and surgery only ($P < 0.05$).
†One-way analysis of variance: There was a significant difference in four groups ($P < 0.05$).

a similar result, we tentatively concluded that early detection of CIS plus conization would avoid any additional years of suffering from living with very dissatisfied HQROL.

Our study does, however, have the following limitations: First, in an ideal condition, all the HRQOL measurements should be performed for each subject and followed longitudinally

Table 3 – Regression coefficients ($\hat{\beta}$) and standard error (in parentheses) based on construction of the mixed-effects model for each facet and domain of the WHOQOL-BREF in patients with cervical cancer.

Domain	Facet	Treatment (reference: Carcinoma in situ postconization)			Education (≥9 y/<9 y)	Renal disease (yes/no)
		Surgery only	Surgery plus chemotherapy or radiotherapy	Chemotherapy or radiotherapy only		
Physical		−5.53 ± 1.85*	−5.08 ± 1.93†	−4.94 ± 2.62		
Psychological		−3.89 ± 1.97	−5.29 ± 2.07†	−3.56 ± 2.81	4.21 ± 1.82†	
Physical	Pain and discomfort	−0.40 ± 0.12*	−0.57 ± 0.13*	−0.32 ± 0.17		
	Mobility	−0.30 ± 0.11†	−0.23 ± 0.11†	−0.37 ± 0.15†		
	Sleep and rest				0.23 ± 0.11†	−0.77 ± 0.33†
	Activities of daily living	−0.17 ± 0.08†	−0.16 ± 0.08	−0.15 ± 0.11		
	Working capacity	−0.04 ± 0.09	−0.25 ± 0.09†	−0.14 ± 0.13		
Psychological	Thinking, memory and concentration	−0.19 ± 0.10	−0.25 ± 0.10†	−0.29 ± 0.14†		
	Self-esteem	−0.08 ± 0.09	−0.19 ± 0.09†	−0.03 ± 0.13		
	Negative feelings	−0.39 ± 0.13*	−0.29 ± 0.14†	−0.33 ± 0.19		
Social	Sexual life	−0.13 ± 0.10	−0.21 ± 0.10†	−0.14 ± 0.15		
Environment	Opportunities for acquiring new skills					−0.85 ± 0.27†

WHOQOL-BREF, World Health Organization Quality of Life–brief version.
* $P < 0.005$.
† $P < 0.05$.

throughout life, but one must wait several decades to complete such studies. We took an alternative approach, which was to recruit cross-sectional, consecutive subjects from a single medical center and clinic by assuming that they were randomly drawn from all the prevalent patients with cervical cancer [22]. Because all these patients were able to come to our clinic and their conditions at interview were generally good enough for them to finish the interview, our results may be an overestimation of the HRQOL of patients with ICC and may underestimate the potential benefit of early detection. Because our reference subjects were taken from CIS postconization, the comparison of contrasted populations may not be biased too much. Second, because the quantification of decreased HRQOL scores must be communicated with the lay person, we have tried to conceptualize the chronic proportional decrease in HRQOL item score to be equivalent to the duration of living with a very dissatisfied condition, for example, the item sexual life, with additional assumptions similar to the conceptualization of quality-adjusted life-year [27]. Perhaps it would be better if such a measure of subjective preference for a specific item could be quantified through the contingent valuation method and converted to a monetary value [28] to become more user-friendly, which would require more studies in the future.

Conclusions and Policy Implications

Early detection of cervical cancer at the CIS stage not only saves about 6.48 years of life loss but also prevents chronic reduced satisfaction of HRQOL in the physical and psychological domains as well as sexual life, which is tremendous considering that the average lifespan for an invasive cancer is 20 years. In the future, researchers may consider how much subjects are willing to pay to estimate the monetary value of the durations of living under very dissatisfied HRQOL [28], especially for the item related to sexual life.

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Supplemental Materials

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